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EXAMINER	
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ART UNIT	PAPER NUMBER
1627	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,713	SCHELLER ET AL.	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *16,17,24-55,57,58,60,62,64 and 68-78* is/are pending in the application.

5a) Of the above claim(s) *16,36 and 68-77* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *17,24-35,37-55,57,58,60,62,64 and 78* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/11/2011, 7/19/2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response to the non-final office action dated 4/19/2011 is acknowledged. Claims 1-15, 18-23, 56, 59, 61, 63, 65-67 have been cancelled. Claims 16, 36, 68-77 are withdrawn from consideration. Claims 35, 58, 60, 62 and 64 have been amended. Claims 16, 17, 24-55, 57, 58, 60, 62, 64, 68-78 are pending. Claims 17, 24-35, 37-55, 57, 58, 60, 62, 64, 78 are examined based on the merits herein.

Response to Remarks/Arguments

Applicants' arguments regarding the ODP rejections have been fully considered but found not to be persuasive. Applicants' state that they may elect to argue to overcome this ground of rejection or to provide a terminal disclaimer (to the extent necessary) once the present claims have been found to be otherwise allowable and/or once the '699 or '997 application issues as a patent. Applicants' arguments to the rejections are addressed in the Response to Arguments section below. Applicants' arguments regarding the 103(a) rejections have been fully considered and found not to be persuasive. The ODP and 103(a) rejections are maintained and are given below for Applicants' convenience. The action is made Final.

Information Disclosure Statements

The information disclosure statements (IDS) filed on 7/19/2011 and 8/11/2011 (with the full text journals of Beaulieu, Belluzzi and Muscat) are in compliance with the provisions of 37 CFR 1.97. Accordingly, the IDS is being considered by the Examiner.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 17-35, 37-67 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10, 13-20, 24-47, 60-71, 83 of copending Application No. 10/565,699. Although the conflicting claims are not identical, they are not patentably distinct from each other because both teach a method of treating depression comprising administering rotigotine. Claims 17-25, 35, 37-55, 57, 58, 60, 62, 64 of the instant application teach a method of treating depression comprising administering 5,6,7,8-tetrahydro-6- [propyl- [2-(2-thienyl)ethyl] amino]- 1-naphthol or a physiologically acceptable salt thereof that includes the s-isomer rotigotine (elected species) and additional drugs that include antidepressants, antipsychotics, anxiolytics, anti-migraine and sedatives. Claims of the co-pending

application '699 teach a method of treating depression comprising administering rotigotine and additional drugs that include antidepressants, antipsychotics, anxiolytics, anti-migraine and sedatives.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 17, 30, 37, 51-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 5, 18, 23, 24, 27 and 28 of copending Application No. 11/060,997. Claims 17, 30, 37, 51-55 of the instant application teaches a method of treating depression comprising administering 5,6,7,8-tetrahydro-6- [propyl- [2-(2-thienyl)ethyl] amino]- 1-naphthol or a physiologically acceptable salt thereof that includes the s-isomer rotigotine (elected species), transdermal administration of the compound at a dosage amount of 0.5-50 mg/day. Claims 15, 18, 23, 24, 27 and 28 of the co-pending application ('997) teaches a method for treatment or prophylaxis of dopaminergic cell loss in a subject suffering from or susceptible to a disease associated with increased dopaminergic cell loss, comprising administration of rotigotine, or a salt or prodrug thereof to the subject and wherein the subject has one or more clinical symptoms selected from the group consisting of smell disorder, depression, sleep disorder etc., transdermal administration of the compound at a dosage amount of 0.05-50 mg/day.

It would have been obvious to a person of ordinary skill in the art at the time of the invention to have used rotigotine in treating depression from the claims 5, 18, 23, 24, 27 and 28 of co-pending application '997 because the claims teaches a method for

treatment or prophylaxis of dopaminergic cell loss in a subject suffering from or susceptible to a disease associated with increased dopaminergic cell loss, comprising administration of rotigotine, or a salt or prodrug thereof to the subject and wherein the subject has one or more clinical symptoms selected from the group consisting of smell disorder, depression, sleep disorder etc. Thus it would be obvious to a person of ordinary skill in the art that administration of rotigotine is useful in treating a clinical symptom such as depression in a subject.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 17, 24-34, 37-55, 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nichols et al. (U.S. 4,501,890) in view of Pfeiffer (Drugs Aging, 2002, vol. 19, no. 8, p. 561-570) and (Lauterback et al. (U.S. 2003/0027793).

Nichols et al. teach that the compounds of Formula III and IV are dopamine D2 agonist and are substantially devoid of other agonist or antagonist blocking activities. As D2 agonists, the compounds are useful in treating Parkinson's syndrome and depression in mammals (see abstract and column 3, lines 20-26).

The reference does not teach that rotigotine treats any type of depression (claims 25-28, 38-50) in humans (claim 24) or that rotigotine is administered parenterally, transdermally or mucosally (claim 30). Nichols et al. also does not teach the amounts of rotigotine to be administered (claim 34, 51-55).

Pfeiffer teaches that rotigotine is a known D2 receptor agonist and is a well tolerated candidate for transdermal Parkinson's disease treatment (see page 566, column 2, 3.3 Rotigotine, first paragraph)

Lauterback teaches a silicon based transdermal therapeutic system containing 0.1 to 3.15 mg/cm^2 of rotigotine as active ingredient for the treatment of Parkinson's disease (see abstract) wherein said transdermal therapeutic system induces a mean plasma concentration of rotigotine in the range of 0.4 to 2 ng/ml 24 h after administration [0030]. The reference further teaches that rotigotine is a dopamine receptor agonist and psychological disorder such as depression may also accompany Parkinson's disease (para 0002). The reference teaches daily dosages of 4.5, 9.0 and 13.5 and 18 mg patches can be administered (para 0045). The reference teaches

silicone-based transdermal therapeutic system with the silicone compound as a pressure sensitive adhesive or a mixture thereof forming a matrix in which the other components of the transdermal system are embedded (para 0017).

A person of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Nichols et al. and the compound rotigotine to treat any type of depression in humans because of the following teachings: 1) Nichols et al. provides the teaching that D2 agonist treat depression and Parkinson's disease; 2) Pfeiffer teaches that rotigotine is a known D2 agonist and well tolerated for transdermal Parkinson's disease in humans; 3) Lauterback teaches rotigotine in treating Parkinson's disease and further teaches that depression may also accompany Parkinson's disease. Thus, since it is known that D2 agonist treat both depression and Parkinson's disease, one skilled in the art would be motivated to try a known effective D2 agonist that treats Parkinson's disease to also treat any type of depression or depression associated with Parkinson's disease. It would have been obvious to one having ordinary skill in the art at the time of the invention to have formulated as an ointment or a plaster having the active ingredient rotigotine for transdermal administration in treating depression because Lauterback et al. teaches transdermal therapeutic system comprising rotigotine and further teach the dosage amounts for administration to a patient. Accordingly, one having ordinary skill in the art would have been motivated to administer the drug transdermally in the claimed amounts because it has been shown in the prior art that such formulation is possible and the drug dosage claimed is a safe amount. Though Lauterback et al. do not explicitly teach establishment

of substantial constant plasma level of rotigotine upon administration for treating depression the reference teaches a mean plasma concentration of rotigotine in the range of 0.4 to 2 ng/ml 24 h after administration. Also, the pharmaceutical forms, e.g., sustained release, immediate release etc. are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations. A person of ordinary skill in the art at the time of the invention would have been motivated to have a controlled release of the drug is to eliminate potential under and over dosing, maintain the drug levels within a desired range of concentration, the need for fewer administration and for increased patient compliance. Despite obvious differences in etiology, many of the conditions including Parkinson's, Alzheimer's disease, brain tumor, epilepsy etc. share depression as a common clinical symptom. Depression is a symptom associated with many diseases and the diseases associated with depression or the types of depression are irrelevant if depression can be treated by administration of a drug.

Claims 35 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nichols et al. (U.S. 4,501,890) in view of Pfeiffer (Drugs Aging, 2002, vol. 19, no. 8, p. 561-570) and (Lauterback et al. (U.S. 2003/0027793) as applied to claims 10-15, 17, 30, 32-44 above and in view of Maj (US 6,255,329).

Nichols et al. in view of Pfeiffer and Lauterback et al. teachings discussed as above.

The references do not teach addition of one or more antidepressants to compound of formula of claim 17 in treating depression.

Maj teaches treatment of depression in patients comprising administering pramipexole and sertraline (see abstract, col. 4, claim 10). Maj teaches that in combination therapy, the agents can be co-administered separately or as components of a single pharmaceutical dosage form and the drugs can be in different dosage forms (col.2. lines 11-30).

It would have been obvious to one having ordinary skill in the art to treat depression comprising administering compound of formula of claim 17, including rotigotine (elected species) along with one or more antidepressant , sertraline (elected species) in treating depression because of the teachings of Maj. Maj teaches treating depression comprising administering pramipexole (useful for treating Parkinson's disease) and sertraline. Rotigotine, the elected species is known in the art to treat Parkinson's disease (Lauterback). One having ordinary skill in the art would have been motivated to use rotigotine for another drug (pramipexole) used in Parkinson's disease in combination with sertraline in treating depression because of expectation of therapeutic benefits, synergistic or additive effects. It would have been obvious to one having ordinary skill in the art at the time of the invention to have administered one of the additional active ingredients in separate dosage forms by the same or different routes at the same or different times because of Maj's teachings. Maj teaches that in treating depression with sertraline the agents can be co-administered separately or as components of a single pharmaceutical dosage form and the drugs can be in different dosage forms. Also, administering another anti-depressant would be obvious because both compounds would be used to treat depression. "It is prima facie obvious to

combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ....[T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). See also In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960); Ex parte Quadranti, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992); and In re Geiger, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987). Also, it is well within the skilled medical professional to determine suitable dosing regimens. It would have been customary for an artisan of ordinary skill to determine the optimal dosage of the drug in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of route of delivery, dosage regimens would have been obvious at the time of applicant's invention.

Claim 58 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nichols et al. (U.S. 4,501,890) in view of Pfeiffer (Drugs Aging, 2002, vol. 19, no. 8, p. 561-570) and (Lauterback et al. (U.S. 2003/0027793) as applied to claims 10-15, 17, 30, 32-44 above and in view of Marquis (U.S. 6,350,773) and Timmerman (chapter 9, E J of pharmacology, 181, 1989, 253-60).

Nichols et al. in view of Pfeiffer and Lauterback et al. teachings discussed as above.

The references do not teach addition of one or more antipsychotics to compound of formula of claim 17 in treating depression.

Marquis teaches a method and composition for the treatment of depression comprising the combination of a D2/D3 agonist and an antipsychotic such as thioridazine (i.e. an anxiolytic), fluphenazine, clozapine, haloperidol, thioridazine, risperidone and olanzapine (see column 1, lines 13-20; claims 3, 6 and 10). The combination can be in a unitary form or separately for simultaneous, separate or sequential administration (see paragraph 4, lines 1-8 and lines 55-63).

It would have been obvious to one having ordinary skill in the art to treat depression comprising administering compound of formula of claim 17, such as rotigotine (elected species) along with an antipsychotic agent, clozapine (elected species) in treating depression because of the teachings of Marquis. Marquis teaches treating depressive disorder comprising administering anti-psychotic agents including clozapine and D2/D3 agonist. One having ordinary skill in the art would have been motivated to use rotigotine in combination with an anti-psychotic drug such as clozapine because clozapine has been shown to be useful in combination anti-depressant therapy. A person of ordinary skill in the art at the time of the invention would have been motivated to use rotigotine (another D2 agonist) for another D2 agonist along with clozapine in treating depression in expectation of similar or better therapeutic benefits. Also, Timmerman (chapter 9, E J of pharmacology, 181, 1989, 253-60) teaches N-0437 (rotigotine) as an antipsychotic drug. One having ordinary skill in the art would have been motivated to administer one anti-psychotic drug (rotigotine) for clozapine in Marquis's method of treating psychotic depression treatment in expectation of similar and or better therapeutic benefits of treating depression.

Claim 58 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nichols et al. (U.S. 4,501,890) in view of Pfeiffer (Drugs Aging, 2002, vol. 19, no. 8, p. 561-570) and (Lauterback et al. (U.S. 2003/0027793) as applied to claims 10-15, 17, 30, 32-44 above and in view of Hrdlicka (Eur Psychiatry, 2002, 17) and Timmerman (chapter 9, E J of pharmacology, 181, 1989, 253-60).

Nichols et al. in view of Pfeiffer and Lauterback et al. teachings discussed as above.

The references do not teach addition of one or more antipsychotics to compound of formula of claim 17 in treating depression.

Hrdlicka teaches combination of clozapine and maprotiline (a tricyclic antidepressant) in refractory psychotic depression treatment. The reference teaches that clozapine is antipsychotic agent and when administered along with maprotoline to a patient with recurrent depressive disorder.

It would have been obvious to one having ordinary skill in the art to treat depression comprising administering compound of formula of claim 17, such as rotigotine (elected species) along with an antipsychotic agent, clozapine (elected species) in treating depression because of the teachings of Hrdlicka. Hrdlicka teaches treating depressive disorder comprising administering clozapine and maprotiline (a tricyclic antidepressant). One having ordinary skill in the art would have been motivated to use rotigotine in combination with an anti-psychotic drug such as clozapine because clozapine has been shown to be useful in combination anti-depressant therapy. A person of ordinary skill in the art at the time of the invention would have been motivated

to use rotigotine along with clozapine in treating depression in expectation of similar or better therapeutic benefits as obtained with clozapine in treating depression. Also, Timmerman (chapter 9, E J of pharmacology, 181, 1989, 253-60) teaches N-0437 (rotigotine) as an antipsychotic drug. One having ordinary skill in the art would have been motivated to administer one anti-psychotic drug (rotigotine) for clozapine in Hrdlicka's method of treating psychotic depression treatment in expectation of similar and or better therapeutic benefits of treating depression.

Claim 60 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nichols et al. (U.S. 4,501,890) in view of Pfeiffer (Drugs Aging, 2002, vol. 19, no. 8, p. 561-570) and (Lauterback et al. (U.S. 2003/0027793) as applied to claims 10-15, 17, 30, 32-44 above and in view of Rimpler et al. (US 2003/0180332 A1).

Nichols et al. in view of Pfeiffer and Lauterback et al. teachings discussed as above.

The references do not teach addition of one or more sedatives to compound of formula of claim 17 in treating depression.

Rimpler et al. teach that rotigotine (N-0923) and its metabolites and prodrugs can be administered with other agents such as diphenhydramine (see paragraphs 89, 110 and 119).

It would have been obvious to one having ordinary skill in the art to treat depression comprising administering compounds of formula of claim 17, such as rotigotine along with a sedative agent, such as diphenhydramine (elected species) in combination therapy of treating depression because Rimpler teaches rotigotine can be

administered with other agents including diphenhydramine. One having ordinary skill in the art would have been motivated to use a sedative agent such as diphenhydramine along with an antidepressant in combination therapy in treating depressive patients is to help the patients and improve the quality of sleep in the patients.

Claim 60 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nichols et al. (U.S. 4,501,890) in view of Pfeiffer (Drugs Aging, 2002, vol. 19, no. 8, p. 561-570) and (Lauterback et al. (U.S. 2003/0027793) as applied to claims 10-15, 17, 30, 32-44 above and in view of Kupfer (Ann Clin Psychiatry, 1999, 11(4), 267-76) and Cook et al. (2002/0177626).

Nichols et al. in view of Pfeiffer and Lauterback et al. teachings discussed as above.

The references do not teach addition of one or more sedatives in treating depression.

Kupfer teaches that depressed patients often report problems sleeping and epidemiologic evidence suggests that insomnia may precede the onset of depression (see Abstract).

It would have been obvious to one having ordinary skill in the art to treat depression comprising administering compounds of formula of claim 17, such as rotigotine along with a sedative agent, such as diphenhydramine (elected species) in combination therapy of treating depression because of the teachings of Kupfer. Kupfer teaches that depressed patients often report problems sleeping and it is known in the art that diphenhydramine is a sedative (US 20020177626). One having ordinary skill in

the art would have been motivated to use a sedative agent along with an antidepressant in combination therapy in treating depressive patients is to help the patients and improve the quality of sleep in the patients.

Claim 62 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nichols et al. (U.S. 4,501,890) in view of Pfeiffer (Drugs Aging, 2002, vol. 19, no. 8, p. 561-570) and (Lauterback et al. (U.S. 2003/0027793) as applied to claims 10-15, 17, 30, 32-44 above and in view of Zimmerman et al. (Am J Psychiatry 160:504-512, March 2003) and (Lehmann, *Neuropsychobiology* 1989;21:197-204, Abstract)

Nichols et al. in view of Pfeiffer and Lauterback et al. teachings discussed as above.

The references do not teach addition of one or more anxiolytics in treating depression.

Zimmerman teaches that compared to the depressed patients without generalized anxiety disorder, the depressed patients with modified generalized anxiety disorder had higher levels of suicidal ideation; poorer social functioning; a greater frequency of other anxiety disorders, eating disorders, and somatoform disorders (See abstract).

It would have been obvious to one having ordinary skill in the art to treat depression comprising administering compounds of formula of claim 17, such as rotigotine along with an anxiolytic agent, such as fluspirilene in combination therapy of treating depression because the prior art teachings teach that the depressed patients with modified generalized anxiety disorder had higher levels of suicidal ideation; poorer

social functioning; a greater frequency of other anxiety disorders, eating disorders, and somatoform disorders. Fluspirilene is known in the art as an anxiolytic agent (Lehmann, *Neuropsychobiology* 1989;21:197-204, Abstract). One having ordinary skill in the art would have been motivated to use an anxiolytic agent along with an antidepressant in combination therapy in treating depressive patients to provide therapeutic benefits for anxiety disorder.

Claim 64 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nichols et al. (U.S. 4,501,890) in view of Pfeiffer (Drugs Aging, 2002, vol. 19, no. 8, p. 561-570) and (Lauterback et al. (U.S. 2003/0027793) as applied to claims 10-15, 17, 30, 32-44 above and in view of document, Links between Depression and Migraine (5/19/2003) and Livingstone et al. (US 2003/0225002).

Nichols et al. in view of Pfeiffer and Lauterback et al. teachings discussed as above.

The references do not teach addition of one or more anti-migraine in treating depression.

Links between Depression and Migraine document teaches that risk of migraine in individuals with pre-existing major depression was three times higher than in individuals with no history of depression and the risk of major depression in persons with pre-existing migraine was more than fivefold higher than in people with no history of headaches.

It would have been obvious to one having ordinary skill in the art to treat depression comprising administering compounds of formula of claim 17, such as

rotigotine along with an anti-migraine agent, such as almoptriptan in combination therapy of treating depression because the prior art teachings teach the connection between migraine and depression. Almotriptan is known in the prior art as an anti-migraine agent (US 20030225002). The document Links between Depression and Migraine teaches that patients with depression had higher risk of migraine. One having ordinary skill in the art would have been motivated to use an anti-migraine agent along with an antidepressant in combination therapy in treating depressive patients to provide therapeutic benefits for migraine.

Response to Arguments

(1) ODP rejections:

(i) 10/565,699 – Applicants argue that Claim 17 is not limited to a "method of treating depression comprising administering rotigotine" and does not include a limitation for "additional drugs that include antidepressants, antipsychotics, anxiolytics, anti-migraine and sedatives." Furthermore, Claim 28 of the '699 application is not directed to method of treating depression by administering rotigotine. Rather, Claim 9 of the '699 application, from which Claim 28 depends, is a combination of (a) rotigotine or a metabolite, prodrug or physiologically acceptable salt thereof, (b) one or more additional active ingredients comprising one or more antidepressants, antipsychotics, sedatives, anxiolytics and/or anti-migraine agents. Claim 28 of the '699 application further recites wherein the one or more additional active ingredients comprise one or more antidepressants and a Markush group of antidepressants.

In response, Claim 17 method is towards treating depression comprising administering 5,6,7,8-tetrahydro-6- [propyl- [2-(2-thienyl)ethyl] amino]- 1-naphthol or a physiologically acceptable salt thereof that includes the s-isomer rotigotine (elected species) and claims 35, 57, 58, 60, 62, 64 include additional active ingredients such as antidepressants, antipsychotics, anxiolytics, anti-migraine and sedatives in combination. Claims 10, 27, 60-71 of the copending application '699 teach a method of treating depression comprising administering rotigotine and additional drugs that include antidepressants, antipsychotics, anxiolytics, anti-migraine and sedatives. Although the conflicting claims are not identical, they are not patentably distinct from each other because both teach a method of treating depression comprising administering rotigotine and additional active drugs including antidepressants, antipsychotics, anxiolytics, anti-migraine and sedatives. Thus the rejection is proper and maintained.

(ii) 11/060,997 – Applicants' argue that the claimed method in '997 is not towards treating depression.

In response, Claims 15 and 18 teaches a method for treatment or prophylaxis of dopaminergic cell loss in a subject suffering from or susceptible to a disease associated with increased dopaminergic cell loss, comprising administration of rotigotine, or a salt or prodrug thereof to the subject and wherein the subject has one or more clinical symptoms selected from the group consisting of smell disorder, depression, sleep disorder etc. Thus it would have been obvious to a person of ordinary skill in the art from '997 that administration of rotigotine is useful in treating a clinical symptom such as depression in a subject.

(2) 103(a) rejections:

(i) Nichols in view of Pfeiffer and Lauterback:

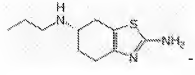
Applicants' argue that "the D2 agonist used to treat Parkinson's disease, APO, failed to treat depression. Wang concluded that APO's "excessive stimulation of D~ receptor may participate in the failure of coping behavior leading to learned helplessness and therefore in the pathophysiological mechanisms underlying the development of depression." Accordingly, the evidence of record exemplifies that a D2 agonist and compound used in treating Parkinson's disease, like APO, can fail to treat depression, and for this reason alone, the Office Action's "motivation to combine" statement is insufficient to support a presumption of prima facie obviousness".

In response, APO is not a D2 agonist but is an agonist for the dopaminergic D1 and D2 receptors (see p 64, col.1, lines 1-2). The reference Wang (Chinese J Physiol. 2007) in p 67 clearly teaches that APO activates both D1 and D2 receptor when administered in high dose but mainly stimulates the dopaminergic autoreceptor when given at low dose, causing an inhibition of dopaminergic functions, the biphasic effects of APO on learned helpless behavior displayed in the present study, which increased the avoidance at 0.5 mg/kg but facilitated the failure at higher dose (p 67, col. 1, para 3, lines 1-4). Accordingly, even the dopaminergic effects of the compound APO is based on the concentration administered. The studies by Wang do not indicate that APO is a D2 selective agonist and do not teach that it fails to treat depression. On the other hand rotigotine at the time of the invention was known to be a D2 agonist. Belluzzi et al.(see abstract), Pfeiffer (see page 566, column 2, 3.3 Rotigotine, first paragraph) all teach that

rotigotine is a D2 agonist. Thus, at the time of the invention one skilled in the art would be motivated to use a D2 agonist such as rotigotine to treat depression based on the teaching of Nichols et al., Pfeiffer and Lauterback. Further, Marquis teaches that a D2/D3 agonist can treat depression (see column 1, lines 13-20). In regards to Wang et al., since at the time of the invention, rotigotine was known to be a D2 agonist, particularly a 15:1 ratio selection of D2 over D1 (see Belluzzi et al. abstract), one skilled in the art would not expect an excessive stimulation of the D1 receptor.

Applicants' argue that Nichols' Compounds are (1) structurally different and (2) do not share the same receptor profile or D2 agonist activity as rotigotine.

In response, there are D2 agonists that are structurally dissimilar but known to be useful for depression. Corrigan et al. and Muscat (Biological Psychiatry, May 1992, vol. 31, issue 9, pp. 937-946, abstract provided) also teach of other compounds with different structures that treat depression, but are D2 agonists. Corrigan further teaches pramipexole, a synthetic aminothiazole derivative is dopamine D2 receptor agonist (structure given below) that currently is approved for use in Parkinson's disease (see p 59, col. 1, para 2). It is within the skill of the art to test a compound that has the same mechanistic action to treat a condition, in which in this case is depression.



- pramipexole

- (U.S. 4501890)

The structures of the above compounds are structurally different yet both are D2 agonists.

Applicants' argue that contrary to the compounds reported in Nichols, rotigotine is not substantially devoid of other agonist or antagonist activity, and further rotigotine demonstrates a preference for the D3 receptor not the D2 receptor. Applicants' in p 7, para 1 argue that one of ordinary skill in the art, without the knowledge of the full receptor profile, could predict effectiveness in rotigotine treating depression.

In response to Applicants' arguments, rotigotine at the time of the invention was known to be a D2 agonist. Belluzzi et al.(see abstract), Pfeiffer (see page 566, column 2, 3.3 Rotigotine, first paragraph) all teach that rotigotine is a D2 agonist. Thus, at the time of the invention one skilled in the art would have known rotigotine as a D2 agonist and would have been motivated to use a D2 agonist such as rotigotine to treat depression based on the teaching of Nichols et al., Pfeiffer and Lauterback.

Applicants' argue that Lauterback and Pfeiffer do not provide any motivation and treating a disease such as Parkinson's does not support the conclusion that the agent can also treat each symptom of the disease, Lauterback does not teach rotigotine has anti-depressive properties.

In response, Pfeiffer teaches that rotigotine is a known D2 receptor agonist. The primary reference Nichols teaches D2 agonist compounds that are useful in treating Parkinson's disease and in treating depression. Thus, the method of treating depression and Parkinson's disease is known in the art to be effective through the D2 agonistic pathway. Pfeiffer's teachings where rotigotine is taught as a D2 receptor agonist, Lauterback where rotigotine is taught to be useful in treating Parkinson's disease when combined with Nichols teachings provide suggestion and motivation to a person of

ordinary skill in the art to try a D2 agonist (rotigotine), known to be useful in treating Parkinson's to treat for depression

Applicants' argue that there is no predictability in rotigotine effectively treating depression from the prior art teachings.

In response, there is an obviousness to try and there is expectation of success for rotigotine to have anti-depressive activity because the compound of Nichols and rotigotine are both D2 agonist and treat Parkinson's disease. Thus, the method of treating depression and Parkinson's disease is effective through the D2 agonistic pathway. One skilled in the art would obviously try rotigotine for depression because of its mechanistic action and common therapeutic efficacy for Parkinson's disease as the Nichols compounds. Those, compounds of this type would obviously be combined together and with other anti-depressant compounds in order to effectively treat depression and Parkinson's disease. It is within the skill of the art to test a compound that has the same mechanistic action to treat a condition, in which in this case is depression.

Applicants' in p 7, para 1 argue that one of ordinary skill in the art, without the knowledge of the full receptor profile, could not predict effectiveness in rotigotine treating depression.

In response to Applicants' arguments, rotigotine at the time of the invention was known to be a D2 agonist. Belluzzi et al.(see abstract), Pfeiffer (see page 566, column 2, 3.3 Rotigotine, first paragraph) all teach that rotigotine is a D2 agonist. Thus, at the time of the invention one skilled in the art would have known rotigotine as a D2 agonist.

and would have been motivated to use a D2 agonist such as rotigotine to treat depression based on the teachings of Nichols et al., Pfeiffer and Lauterback.

3. Applicants' argue that there is unreasonable amount of experimentation with no guidance from the cited art and there is no reasonable expectation of success for using rotigotine in treating depression from the cited art.

In response at the time of the invention it was known in the art that rotigotine is a D2 agonist, useful in Parkinson's disease, drugs that have been known as D2 agonists have been found to be useful in treating Parkinson's disease and depression. In addition it was widely known in the art at the time of the invention that depression is a common clinical feature of Parkinson's disease and 40-50% of the patients with Parkinson's are afflicted with depression (see Gotham, J of Neurology, Neurosurgery, 1986, 49, 381-389, Allain, BMJ, 320, p 1287-88, 2000). Accordingly, one skilled in the art at the time of the invention would have found it obvious to choose a drug from the D2 agonists that is useful in treating Parkinson's disease to treat for depression. In this case rotigotine was known in the art to be useful for Parkinson's disease (thus the safety), pharmaceutical composition was known, also known to be D2 agonist. Thus a person skilled in the art would have found rotigotine as one of the lead compounds that has been known to be useful in treating Parkinson's, a D2 agonist to try in treating depression. Based on the facts known about rotigotine at the time of the invention it would have not been an undue experimentation to a person of ordinary skill in the art to have tried rotigotine for treating depression. There is an obviousness to try and expectation of success for rotigotine to have anti-depressive activity because the compound of Nichols and

rotigotine are both D2 agonist and treat Parkinson's disease. Thus, the method of treating depression and Parkinson's disease is effective through the D2 agonistic pathway. One skilled in the art would obviously try rotigotine for depression because of its mechanistic action and common therapeutic efficacy for Parkinson's disease as the Nichols compounds.

4. Rejection under 35 U.S.C. §103(a) over the Alleged 4-Way Combination of Nichols in view of Pfeiffer, Lauterbach and Maj:

Applicants' argue that the facts of the case are not comparable with those of In re Kerkhoven and Maj does not change the conclusion that the claims are obvious over the cited prior art.

The same arguments stated above hold true for Nichols in view of Pfeiffer, Lauterbach. Maj has been cited for disclosure that additional antidepressant like sertraline, an antidepressant in addition to rotigotine (elected species) for the treatment of depression. Maj teaches treating depression comprising administering pramipexole (useful for treating Parkinson's disease) and sertraline. Rotigotine, the elected species is known in the art to treat Parkinson's disease (Lauterback). One having ordinary skill in the art would have been motivated to use rotigotine for another drug (pramipexole) used in Parkinson's disease in combination with sertraline in treating depression because of expectation of therapeutic benefits, synergistic or additive effects. In re Kerkhoven is cited to show that the dosage administration in a combination therapy can be done by separate or simultaneous administration in single composition.

5. Rejection under 35 U.S.C. §103(a) over the Alleged 5-Way Combination of

Nichols in view of Pfeiffer, Lauterbach, Marquis and Timmerman.

Applicants' argue that addition of Marquis to the previous 3-way combination of documents does not change the conclusion that the claims are obvious over the cited prior art.

The same arguments stated above hold true for Nichols in view of Pfeiffer, Lauterbach. Marquis has been cited for disclosure that combination of a D2/D3 agonist and an antipsychotic such as thioridazine (i.e. an anxiolytic), fluphenazine, clozapine, haloperidol, thioridazine, risperidone and olanzapine is useful in treating depression. A person of ordinary skill in the art from Marquis's teachings would have found it obvious to add an anti-psychotic agent clozapine in treating depression to add beneficial therapeutic effects.

6. Rejection under 35 U.S.C. §103(a) over the Alleged 5-Way Combination of Nichols in view of Pfeiffer, Lauterbach, Hrdlicka, and Timmerman.

Applicants' argue that addition of Hrdlicka to the previous 3-way combination of documents does not change the conclusion that the claims are obvious over the cited prior art.

The same arguments stated above hold true for Nichols in view of Pfeiffer, Lauterbach. Hrdlicka teaches treating depressive disorder comprising administering clozapine and maprotiline. A person of ordinary skill in the art from Hrdlicka's teachings would have found it obvious to add an anti-psychotic agent clozapine in treating depression to add beneficial therapeutic effects.

7. Rejection under 35 U.S.C. §103(a) over the Alleged 4-Way Combination of

Nichols in view of Pfeiffer, Lauterbach and Rimpler.

Applicants' argue that addition of Rimpler to the previous 3-way combination of documents does not change the conclusion that the claims are obvious over the cited prior art.

The same arguments stated above hold true for Nichols in view of Pfeiffer, Lauterbach. Rimpler et al. teach that rotigotine (N-0923) and its metabolites and prodrugs can be administered with other agents such as diphenhydramine. A person of ordinary skill in the art from Rimpler's teachings would have found it obvious to add sedative agent diphenhydramine in treating depression to add beneficial therapeutic effects.

8. Rejection under 35 U.S.C. §103(a) over the Alleged 5-Way Combination of Nichols in view of Pfeiffer, Lauterbach, Kupfer, and Cook.

Applicants' argue that addition of Kupfer and/or Cook to the previous 3-way combination of documents does not change the conclusion that the claims are obvious over the cited prior art.

The same arguments stated above hold true for Nichols in view of Pfeiffer, Lauterbach. Kupfer teaches that depressed patients often report problems sleeping and epidemiologic evidence suggests that insomnia may precede the onset of depression and Cook teaches diphenhydramine is a sedative. A person of ordinary skill in the art from Kupfer and Cook teachings would have found it obvious to add sedative agent diphenhydramine in treating depression to cope with the sleeping problems.

9. Rejection under 35 U.S.C. §103(a) over the Alleged 5-Way Combination of

Nichols in view of Pfeiffer, Lauterbach, Zimmerman, and Lehman.

Applicants' argue that addition of Zimmerman and/or Lehman to the previous 3-way combination of documents does not change the conclusion that the claims are obvious over the cited prior art.

The same arguments stated above hold true for Nichols in view of Pfeiffer, Lauterbach. Zimmerman teaches that the depressed patients have generalized anxiety disorder and Lehman teaches fluspirilene as an anxiolytic agent. A person of ordinary skill in the art from Zimmerman and Lehman teachings would have found it obvious to add sedative agent fluspirilene in treating depression to cope with the anxiety problems.

10. Rejection under 35 U.S.C. §103(a) over the Alleged 5-Way Combination of Nichols in view of Pfeiffer and Lauterbach, Medicine News, and Livingston.

Applicants' argue that addition of Medicine News, and/or Livingston to the previous 3-way combination of documents does not change the conclusion that the claims are obvious over the cited prior art.

The same arguments stated above hold true for Nichols in view of Pfeiffer, Lauterbach. Medicine news teaches that risk of migraine in individuals with pre-existing major depression was three times higher than in individuals with no history of depression and Livingston teaches almotriptan as an anti-migraine agent. Thus a person of ordinary skill in the art from Medicine news and Livingston teachings would have found it obvious to add an anti-migraine agent, almotriptan in treating depression to cope with the migraines associated with depression.

Conclusion

No claims are allowed.

The rejection from the previous office action has been maintained. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to UMAMAHESWARI RAMACHANDRAN whose telephone number is (571)272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SREENI PADMANABHAN/
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